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TITLE: Evaluation of Neurophysiologic and Systematic Changes during Aeromedical Evacuation and en Route Care of Combat Casualties in a Swine Polytrauma

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14. ABSTRACT

There is a dearth of knowledge about the effects of long range aero-medical evacuation on injured organs, as well as an emerging published database suggesting clinically significant adverse effects of hypobaria on even healthy tissues. Cabin pressure is equivalent to an altitude around 8,000ft. at which inspired oxygen is sufficient to maintain blood oxygen saturation above 90% in a healthy individual. In combat casualties with multiple injuries this could however compromise oxygen delivery and result in hypoxemia. Additionally, increase in altitude with concomitant decrease in atmospheric pressure allows gas expansion in body cavities. The volume of trapped gas expands by approximately 35% from sea level to an altitude of 8,000 feet. This can expose already vulnerable patients to severe complications. In light of this, a thorough investigation of the effects of hypobaria in clinical settings simulating the most important injury patterns encountered by combat casualties is necessary to optimize treatment efficacy and safety.

During the third year of this project, experiments in swine with Acute Respiratory Distress Syndrome (ARDS) and with Traumatic Brain Injury (TBI) have been completed and results have been presented at National Scientific Meetings. We found that a simulated four hour aeromedical evacuation flight in those models significantly reduced arterial oxygen pressure and increased intrapulmonary shunt fraction in ARDS and significantly reduced cerebral perfusion pressure and brain tissue oxygenation in TBI compared to normobaric conditions. Further studies are indicated to simulate other en route care scenarios and possibly revise casualty evacuation guidelines.

15. SUBJECT TERMS
Aeromedical evacuation, en-route care, hypobaric conditions, hypobaric chamber, swine model

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INTRODUCTION:

Rapid evacuation of combat casualties to definitive care in the United States is practice based on evidence derived from recent military conflicts and has greatly diminished morbidity and mortality among combat casualties. However, not much is known about the effects of long range aero-medical evacuation in hypobaric environments on the physiology and organ function of injured warfighters, thus potentially and unknowingly putting combat casualties at risk during evacuation. Traumatic brain injury (TBI) patients are of particular concern, since small changes in ambient conditions such as cabin pressure and temperature could potentially have detrimental effects on the already vulnerable brain. There is evidence that hypobaria as well as in-flight cabin pressure fluctuations can induce neurological symptoms in otherwise healthy persons due to altitude decompression sickness. This suggests that high altitude hypobaric conditions can have detrimental effects on pulmonary and neurologic outcome and that aero-medical conditions and/or therapeutics can be optimized to attenuate such adverse effects.

Our hypothesis is that hypobaria during simulated long-range aero-medical evacuation has adverse effects on brain blood flow and tissue oxygenation, as well as lung function in swine models of neurotrauma and polytrauma. We plan to investigate the effects of aero-medical evacuation on neurophysiology and lung function in swine models of TBI with and without hemorrhagic shock (HS) and/or ARDS (polytrauma).

BODY:

Tasks 1 (build hypobaric chamber) and 2 (secure IACUC approval) have been completed in Year 1 of this grant. The following two tasks were initiated in Year 2 of the grant and continued during this reporting period of year 3:

Task 3. Animal experiments during normobaric conditions (months 5-28):
Subtask 1. Complete 72 animal experiments in Sham, TBI alone, TBI+HS, ARDS alone, TBI+ARDS and TBI+HS+ARDS groups. Animals will be randomized (months 5-28)
Subtask 2. Hematologic and hematologic analysis of blood samples (months 5-28).
Subtask 3. Necropsy, gross pathology, histopathologic analysis (months 5-28).

Animal experiments have been initiated under normobaric conditions and continue as scheduled.

Task 4. Animal experiments during hypobaric conditions (months 15-39):
Subtask 1. Complete 10 pilot animals to test hypobaric chamber and animal set up for monitoring within the chamber (months15-16).
Subtask 2. Complete 72 animal experiments in Sham, TBI alone, TBI+HS, ARDS alone, TBI+ARDS and TBI+HS+ARDS groups. Animals will be randomized (months 17-39)
Subtask 3. Hematologic and hematologic analysis of blood samples (months 17-39).
Subtask 4. Necropsy, gross pathology, histopathologic analysis (months 17-39).

KEY RESEARCH ACCOMPLISHMENTS:

1. Complete animal experiments with Acute Respiratory Distress Syndrome (ARDS)

ARDS was induced in anesthetized Yorkshire swine via oleic acid infusion, followed by injury-specific in-hospital care over two hours. Once the animal was stable, a 4 hour

aeromedical evacuation was simulated in a hypobaric chamber with atmospheric pressure equivalent to an altitude of 8000 ft. (HYPO, n=9). Control animals were kept at normobaric (ground transport) conditions (NORMO, n=9). Animals were intubated and ventilated with 40% O_2. At 6 hours, animals were euthanized and a full necropsy was performed. Systemic physiology data (vital signs, pulmonary artery catheter parameters, lung function) was collected and blood was analyzed for blood gases, electrolytes and organ function assay indicators.

2. Set up new fluid percussion TBI device for next set of experiments

We received a new fluid percussion device and set up functionality and completed calibration.

3. Animal experiments with TBI alone have been completed:

Anesthetized swine had fluid percussion TBI and injury-specific care over 2 hours, followed by a 4 hour aeromedical evacuation simulated in a hypobaric chamber with atmospheric pressure equivalent to an altitude of 8000 ft. (HYPO, n=6). Control animals were kept at normobaria (NORMO, n=6). At 6 hours, animals were euthanized. Systemic and neurophysiology [brain tissue oxygenation ($pbrO_2$)] data were collected. Blood was analyzed for arterial gases and electrolytes. Repeated-measures ANOVA with $p \leq 0.05$ was considered significant.

REPORTABLE OUTCOMES:

"Evaluation of physiology and lung function in hypobaric conditions during aeromedical evacuation in swine with mild ARDS", Annual Meeting of the American Society of Anesthesiologists, San Diego, CA (October 2015).

"Hypobaria during aeromedical evacuation reduced arterial oxygen pressure and increased pulmonary shunt fraction in swine with ARDS". Military Health System Research Symposium, Ft. Lauderdale, FL (August 2015).

Scultetus A, Haque A, Chun S, Mahon R, Harssema M, Auker C, Moon-Massat P, Malone D, McCarron R. Brain hypoxia is exacerbated in hypobaria during aeromedical evacuation in swine with TBI. Submitted for publication to J Trauma (*under review).*

CONCLUSION:

In this swine model of ARDS and 4 hour simulated aeromedical evacuation, prolonged hypobaria resulted in a significant reduction of arterial oxygen pressure and increased intrapulmonary shunt fraction compared to normobaric conditions. This suggests that hypobaric conditions exacerbate hypoxia and lung injury in swine already under pulmonary compromise after ARDS. Further studies are indicated to simulate other en route care scenarios and possibly revise casualty evacuation guidelines.

In this swine model of TBI, data analysis showed that prolonged hypobaria resulted in a significant reduction in cerebral perfusion pressure, and in reduced brain tissue oxygenation compared to normobaric conditions. These findings may suggest that

hypobaric conditions exacerbate hypoxia in swine already under neurophysiological compromise due to TBI.

REFERENCES:
None.

APPENDICES:

None.

SUPPORTING DATA:

ARDS Experiments:

Baseline parameters were similar in both groups during the in-hospital phase and at the beginning of flight. During flight, pO_2 was significantly lower in HYPO animals (171.8±2.9 mmHg) compared to NORMO (200±1.8 mmHg, $p<0.0001$, Figure 1).

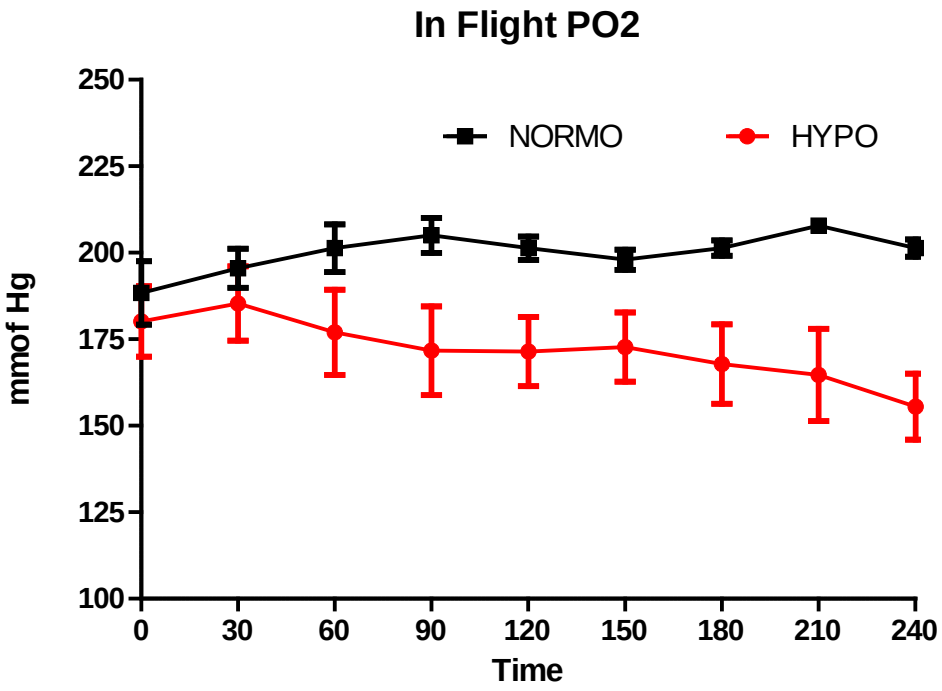


Figure 1: pO_2 during simulated flight compared to normobaric ground conditions.

Capillary oxygen, oxygen delivery and consumption were lower in HYPO animals, though not statistically significant. However, pulmonary shunt fraction (Qs/Qt) was significantly higher in HYPO than in NORMO animals (0.046±0.001 vs. 0.023±0.001 respectively, $p<0.0001$, Figure 2). Organ chemistry and histopathological analyses are pending.

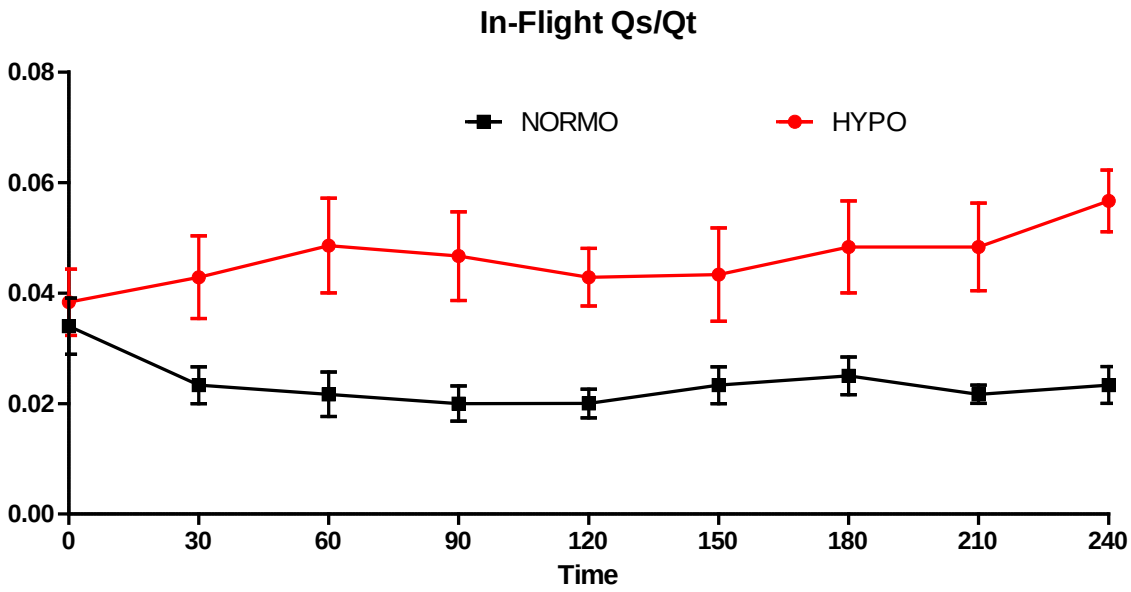


Figure 2: Pulmonary shunt fraction during simulated flight compared to normobaric ground conditions.

TBI experiments:

Results: Baseline parameters were similar in both groups.

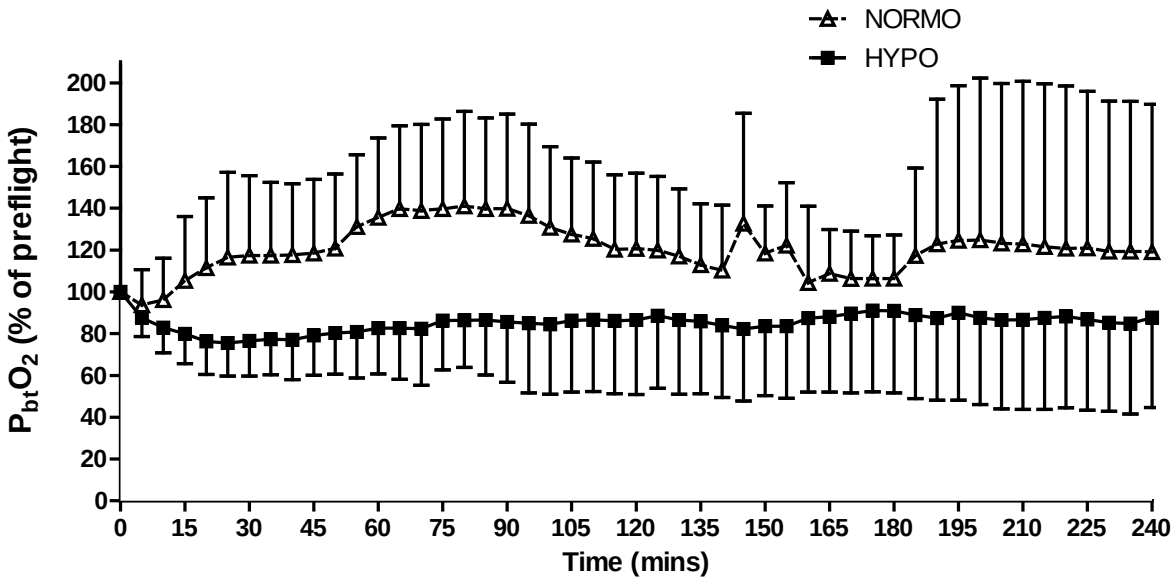


Figure 3: Change in brain tissue oxygen concentration ($P_{bt}O_2$, mean ± SEM) during 4 h simulated transport of swine with TBI at 8,000 ft. altitude (HYPO) or at sea level, 0 ft. (NORMO). Time 0 = BL before transport (sea level). $PbtO_2$ (%) percent change from baseline before flight (BL) was significantly lower in the HYPO group compared to the

NORMO group (p = 0.024; Fig. 1). Specifically, $PbtO_2$ (%) percent change from baseline before flight (BL) was significantly lower from T30 to T105 in the HYPO group compared to the NORMO group (T-Test, p≤ 0.05). The HYPO animals displayed a steady trend towards reduced $PbtO_2$ % change from BL, although this did not reach statistical significance.

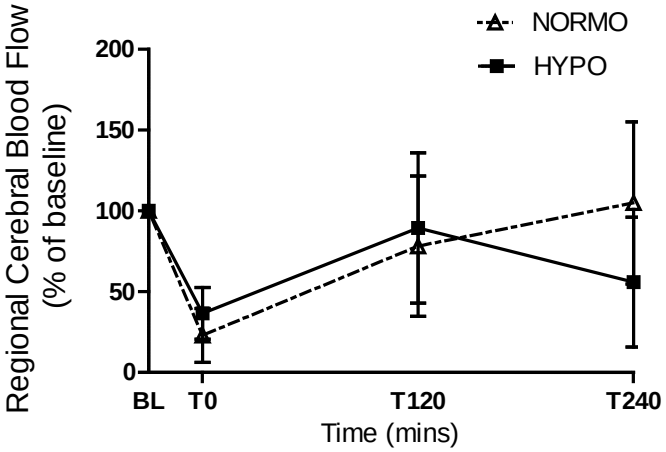
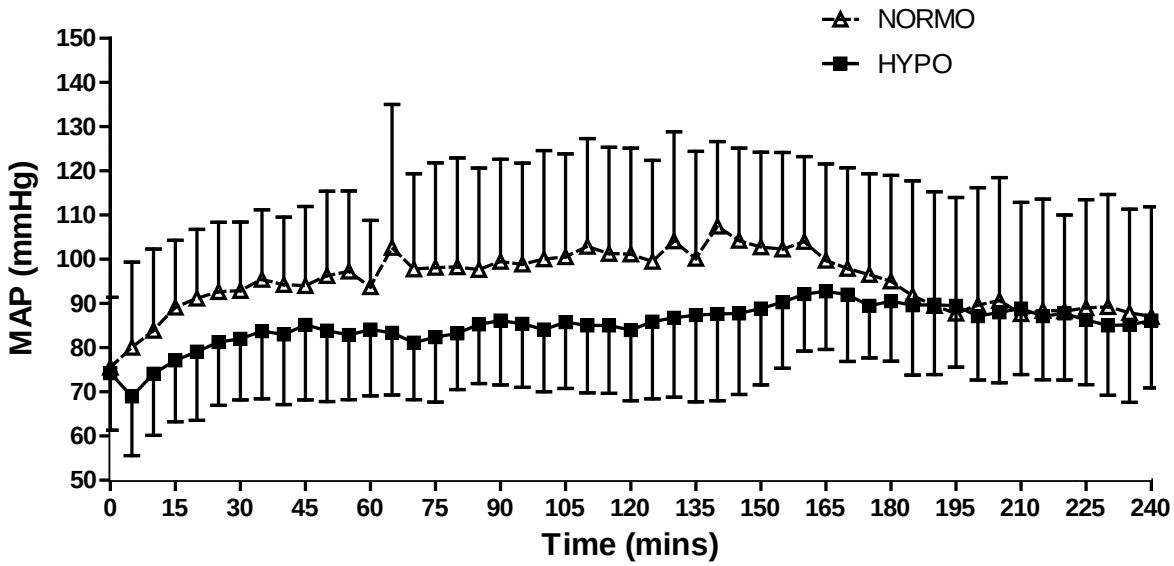
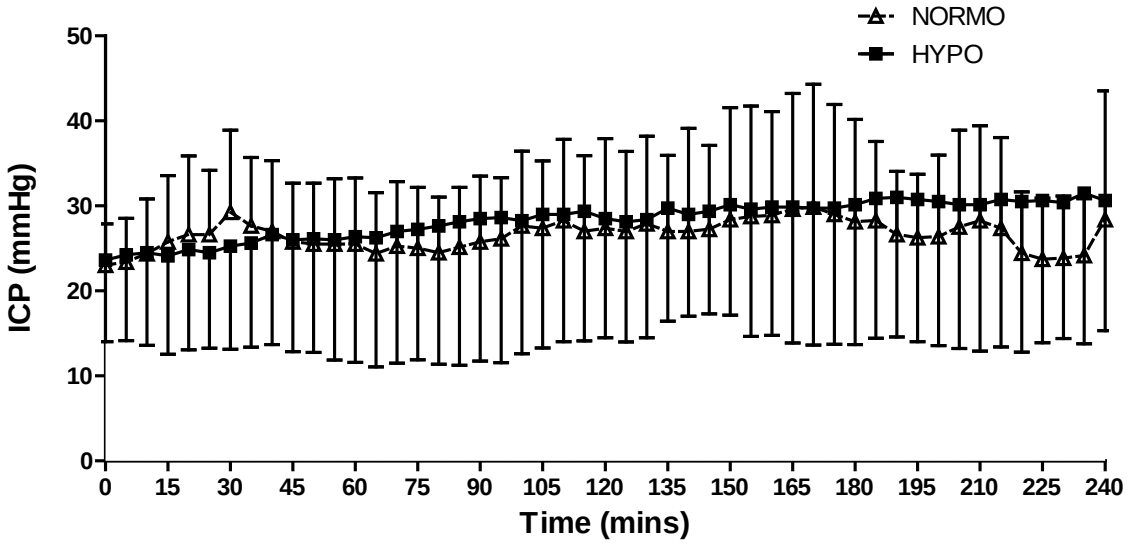


Figure 4: Change in regional cerebral blood flow (rCBF, mean ± SEM) of swine with TBI at 8,000 ft. altitude (HYPO) or at sea level, 0 ft. (NORMO). BL = before injury. T0 = BL before transport (sea level). T120 and T240 = 2 and 4 hours into transport. Regional cerebral blood flow (rCBF) appeared higher in normobaric animals compared to hypobaric animals at the end of the flight, but this difference did not reach statistical significance.

A


NORMO
HYPO
MAP (mmHg)
150
140
130
120
110
100
90
80
70
60
50
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
Time (mins)

B


NORMO
HYPO
ICP (mmHg)
50
40
30
20
10
0
0
15
30
45
60
75
90
105
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165
180
195
210
225
240
Time (mins)

C

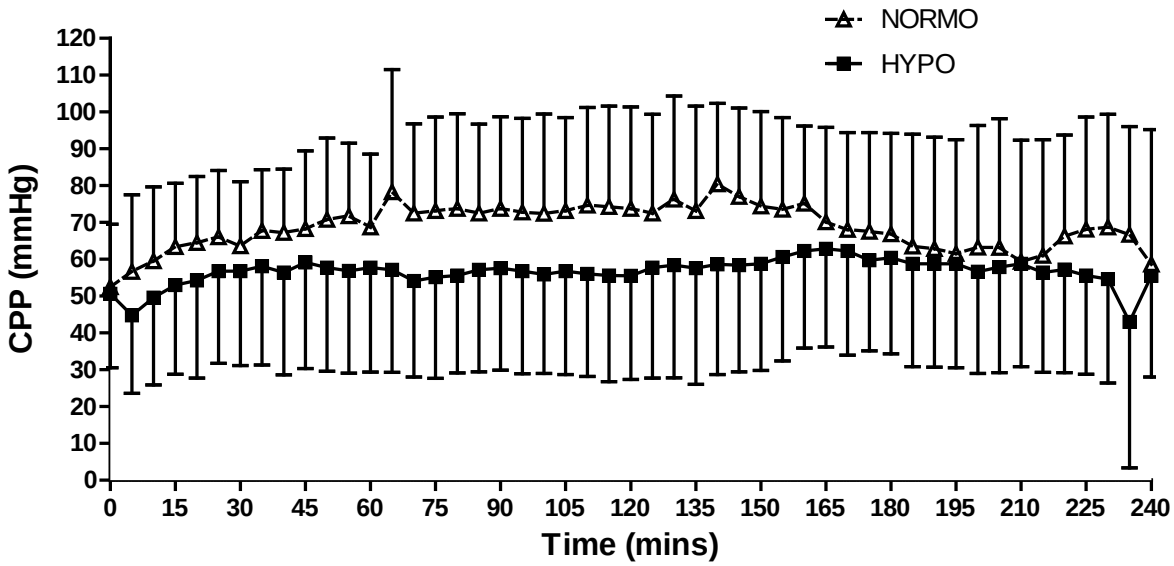

Figure 5: Mean Arterial Blood Pressure (MAP, Panel A), Intracranial Pressure (ICP, Panel B) and Cerebral Perfusion Pressure (CPP, Panel C) during 4 h simulated transport of swine with TBI at 8,000 ft. altitude (HYPO) or at sea level, 0 ft. (NORMO). Mean ± SEM. Time 0 = BL before transport (sea level). ICP was similar in both groups and was not statistically significant (Panel B). There was a significant interaction between group and time for CPP (p=0.032) and MAP (p=0.004; Panels A and C, respectively), which indicates that differences in MAP and CPP between the groups increased over time during the flight. CPP and MAP were also significantly lower from T0 over time in HYPO animals (p=0.037 and p<0.0001, respectively).